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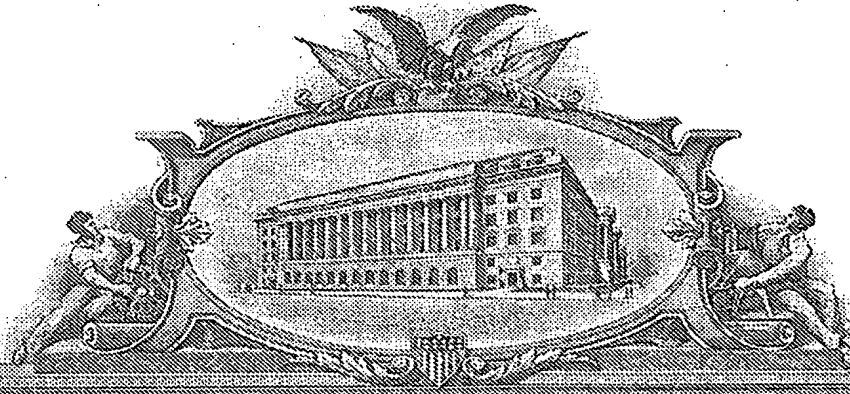
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APPLICATION NUMBER: 10/804,264

FILING DATE: March 18, 2004

RELATED PCT APPLICATION NUMBER: PCT/US05/08839



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18334 U.S. PTO

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	ATAKEM-002-USA
First Inventor	Arnold Takeimoto
Title	Preparations of Encapsulated
Express Mail Label No.	ER 753 238 745 US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO:

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- ☒ Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
Applicant claims small entity status.
See 37 CFR 1.27.
- ☒ Specification [Total Pages 52]
(preferred arrangement set forth below)
- Descriptive title of the invention
- Cross Reference to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to sequence listing, a table,
or a computer program listing appendix
- Background of the invention
- Brief Summary of the invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claim(s)
- Abstract of the Disclosure
- ☐ Drawing(s) (35 U.S.C. 113) [Total Sheets 2]
- Oath or Declaration [Total Sheets 2]
a. ☒ Newly executed (original or copy)
b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 18 completed)
i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting inventor(s)
name in the prior application, see 37 CFR
1.63(d)(2) and 1.33(b).
- ☐ Application Data Sheet. See 37 CFR 1.76

- ☐ CD-ROM or CD-R in duplicate, large table or
Computer Program (Appendix)
- Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
a. ☐ Computer Readable Form (CRF)

b. Specification Sequence Listing on:

i. ☐ CD-ROM or CD-R (2 copies); orii. ☐ Paperc. ☐ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

- ☐ Assignment Papers (cover sheet & document(s))
- ☐ 37 CFR 3.73(b) Statement [Power of Attorney]
(when there is an assignee)
- ☐ English Translation Document (if applicable)
- ☐ Information Disclosure Statement (IDS)/PTO-1449 [Copies of IDS Citations]
- ☐ Preliminary Amendment
- ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
- ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
- ☐ Nonpublication Request under 35 U.S.C. 122
(b)(2)(B)(i). Applicant must attach form PTO/SB/35
or its equivalent.
- ☐ Other:

18. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:

☐ Continuation☐ Divisional☐ Continuation-in-part (CIP)

of prior application No.:

Prior application information:

Examiner

Art Unit

For CONTINUATION OR DIVISIONAL APPS only, The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS

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Name (Print/Type)	GREGORY SHEN		Registration No. (Attorney/Agent)	47940	
Signature			Date	3-18-2004	

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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17497 U.S. PTO
10/804264

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FEE TRANSMITTAL
for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27**TOTAL AMOUNT OF PAYMENT (\$)****Complete if Known**

Application Number	
Filing Date	3-18-2004
First Named Inventor	Arnold Takemoto
Examiner Name	
Art Unit	
Attorney Docket No.	ATAKEN-002-USA

METHOD OF PAYMENT (check all that apply)☒ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None☐ Deposit Account: T8D

Deposit Account Number	
Deposit Account Name	

The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments☒ Charge any additional fee(s) or any underpayment of fee(s)☒ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.**FEE CALCULATION****1. BASIC FILING FEE**

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1001 770	2001 385	Utility filing fee	385
1002 340	2002 170	Design filing fee	
1003 530	2003 265	Plant filing fee	
1004 770	2004 385	Reissue filing fee	
1005 160	2005 80	Provisional filing fee	

SUBTOTAL (1) (\$) 385**2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE**

Total Claims	Extra Claims	Fee from balance	Fee Paid
Independent Claims	-20** =	X	
Multiple Dependent	-3** =	X	

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description
1202 18	2202 9	Claims in excess of 20
1201 86	2201 43	Independent claims in excess of 3
1203 290	2203 145	Multiple dependent claim, if not paid
1204 86	2204 43	** Reissue independent claims over original patent
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)**3. ADDITIONAL FEES**

Large Entity Small Entity

Fee Code (\$)	Fee Code (\$)	Fee Description	Fee Paid
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	1053 130	Non-English specification	
1812 2,520	1812 2,520	For filing a request for ex parte reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	
1252 420	2252 210	Extension for reply within second month	
1253 950	2253 475	Extension for reply within third month	
1254 1,480	2254 740	Extension for reply within fourth month	
1255 2,010	2255 1,005	Extension for reply within fifth month	
1401 330	2401 165	Notice of Appeal	
1402 330	2402 165	Filing a brief in support of an appeal	
1403 290	2403 145	Request for oral hearing	
1451 1,510	1451 1,510	Petition to institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,330	2453 665	Petition to revive - unintentional	
1501 1,330	2501 665	Utility issue fee (or reissue)	
1502 480	2502 240	Design issue fee	
1503 640	2503 320	Plant issue fee	
1460 130	1460 130	Petitions to the Commissioner	
1807 50	1807 50	Processing fee under 37 CFR 1.17(q)	
1808 180	1808 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 770	2809 385	Filing a submission after final rejection (37 CFR 1.129(e))	
1810 770	2810 385	For each additional invention to be examined (37 CFR 1.129(b))	
1801 770	2801 385	Request for Continued Examination (RCE)	
1802 900	1802 900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$)**SUBMITTED BY**

Name (Print/Type)	GREGORY, SHEN	Registration No. (Attorney/Agent)	47940	Telephone	619-248-8645
Signature	<i>G. Shen</i>	Date	3-18-2004		

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

APPLICATION FOR UNITED STATES PATENT

in the name of

Arnold C. Takemoto

of

Immune Nutraceuticals, Inc.

for

**Preparations of encapsulated bioavailable chelating
agents for detoxifying humans and animals**

I hereby certify under 37 CFR 1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office To Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

signature

Gregory H. Shen

name

DATE OF DEPOSIT: 03/18/2004

EXPRESS MAIL NO.: ER 753 238745 US

Preparations of encapsulated bioavailable chelating agents for detoxifying humans and animals

FIELD OF THE INVENTION

This invention relates to preparations comprising chelating agents that are serviceable for the heavy metal detoxification of humans and animals and that can, in non-limiting fashion, be administered orally, parenterally, or transdermally. In non-limiting exemplifications, this invention provides novel preparations of chelating agents encapsulated in micelles or liposomes comprising the triple combination of 1) micelles or liposomes comprising alpha lipoic acid and 2) micelles or liposomes comprising EDTA or other chelators; and furthermore, in different embodiments, 3) magnesium chloride is optionally an additional ingredient in these novel preparations.

RELATED APPLICATIONS

Priority is claimed to provisional application (Ser. No. not yet assigned, filed March 17, 2004, entitled: Detoxification and chelating preparations that can be administered orally, parenterally, and transdermally, and related methods).

BACKGROUND OF THE INVENTION

Toxicity and poisoning.

Heavy metal poisoning is a serious medical problem that is receiving even more emphasis in recent years as the ability to detect toxic metals as well as the ability to understand the detrimental affects associated therewith have progressed compared to the past. Furthermore, it is known that toxic heavy metals such as lead and mercury may very easily enter the body as a consequence of, to name a few examples, accumulated exposure, accidents, environmental pollution, and oral consumption (e.g. food or paint). For example, exposures to lead and mercury are wide-spread and well documented. Poisoning from excessive concentrations of substances that would other wise be beneficial at lower concentrations is also known; e.g. iron poisoning has been reported. Arsenic can get into the body, e.g. as a result of industrial pollution. Also of concern are radioactive toxic heavy metals that pose an additional problem due to their radioactivity. These must be eliminated as quickly as possible, because the ionizing radiations of the radioactive metals pose the risk of tumor induction from their radioactive ionization, including by altering DNA. Toxic heavy metals are also known to concentrate in various organs of the body. Plutonium, for example, usually deposits in the liver, and it is known that as much as 30 to 60% or more of an administered amount of plutonium will oftentimes deposit in the liver. The toxic heavy metal, plutonium in this example, remains in the organ and is only very slowly removed, thereby increasing the potential for tumors.

Summary of challenges with traditional treatments.

- 1) I.v. chelation is expensive, time-consuming, and has poor patient compliance.
- 2) Traditional oral chelation therapies are cheaper, but they are relatively ineffective at their intended purposes, and, at higher doses, are accompanied by side effects. For example, the oral administration of chelating agents by traditional approaches is problematic not only because their poor absorption and bioavailability prevents them from reaching the bodily stores of toxins and heavy metals, but furthermore they can chelate beneficial substances in the digestive tract.
- 3) Using traditional therapies, neither parenterally (e.g. by i.v.) nor orally administered chelating agents are able to enter the intracellular compartments where toxins and heavy metals are also present. Traditional therapies for the parenteral administration of chelating agents using physiologically compatible aqueous solutions (e.g. saline, Ringer's solution, etc.), fail to cause absorption of lipid soluble agents, because of inherent solubility problems.

1) Challenges with i.v. chelation therapies.

Heavy metal detoxification can be accomplished using i.v. chelation with ingredients such as EDTA; this approach has been documented to be effective and safe, and EDTA was approved by the FDA for this use in the 1950's. The ability of i.v. chelation therapy to diminish and even dissolve arterial plaques has also been reported. However, i.v. chelation is very expensive and time-consuming, typically requiring a patient make a series of 20 to 50 visits to a physician's office or hospital (at least 30 visits are typically required), with each

visit often taking from 3-4 hours, during which time the patient is typically seated, and costing up to \$100 or more per visit.

2) Challenges with orally administered chelation therapies.

Oral chelation products are commercially available, and they are marketed as much less expensive alternatives to i.v. chelation therapies. However, EDTA is very poorly absorbed when administered by mouth; and the general consensus is that typically only about five percent is absorbed. Although even that small amount does remove lead from the body, it also been reported to increase the absorption of lead.

Other serious potential problems have been reported as well. For example, it has been reported that the unabsorbed 95 percent of EDTA that remains within the digestive tract, mixes with undigested food and nutrients while passing on out of the body in stool. This unabsorbed EDTA tightly binds to and blocks absorption of many essential nutritional trace elements as it passes through, thereby potentially blocking the uptake of important nutrients such as zinc, manganese, chromium, vanadium, copper, chromium, molybdenum and other essential nutrients, causing deficiencies.

When a chelator such as EDTA enters the body, either by mouth or intravenously, it could possibly remove 10 to 20 times more of the essential nutritional trace elements (such as zinc and manganese) than it does the undesired heavy metals or toxins that are deleterious. When given intravenously, thus bypassing any absorption problems, a full therapeutic treatment of

EDTA can be completed with 20 to 50 daily doses. The replenishment of the lost essential trace elements by dietary supplementation can then take place during the remaining 315+ days of the year after the treatment, when the exogenously administered chelating agent(s) such as EDTA have been excreted or eliminated, and are not present to interfere. Because such a small amount is absorbed by mouth, oral EDTA is often given every day, but for up to 20 times or more as long, to accumulate what is alleged to be an effective dose, and there is no interim opportunity to replenish the essential nutrients that are being continuously blocked and depleted during the chelation therapy.

Thus, the daily administration of chelating agents such as EDTA by mouth may cause progressive deficiencies of zinc, manganese and other essential trace nutrients, which are an essential part of the body's antioxidant defenses. For example, the activity of superoxide dismutase (SOD), a very important intracellular antioxidant, depends on zinc and manganese. By inactivating antioxidant enzymes, the daily intake of chelation agents by mouth may actually worsen the condition of the patients being treated.

Intravenous chelation therapy has been reported to stimulate the release of parathyroid hormone (parathormone) in a pulsatile manner, but orally administered chelation therapies, such as with EDTA, have not. Thus, if that mechanism of action is important to achieve the intended benefit, oral EDTA cannot achieve the goal.

Attempts have been reported to increase the amount of chelating agents that are used in an oral chelation therapy to match the levels that can be achieved when they are administered

intravenously. However, there are many side effects that prevent this approach from being used.

3) Challenges with both oral and i.v. chelation therapies.

The use of chelating agents for the removal of toxic heavy metals is based on their ability to form stable, nonionic, soluble and readily excretable complexes with the metal molecules in the tissues. They have proven valuable because they, in themselves, have a very low toxicity, are able to form soluble, excretable metal chelates within a body, and resist degradation by cell metabolites. However, the serious limitation for the use of chelating agents is that, when introduced into a body, they exist as hydrated anions in the blood plasma. These anions are unable to penetrate cellular membranes. Therefore, only extracellularly deposited toxic metals can be complexed by the chelating agents and removed from the body, whereas intracellularly deposited metals are not complexed by the chelating agent and therefore are not readily removed. Attempts have been made in the past to increase the penetration of chelating agents through cellular membranes such as by the esterification of polyaminopolycarboxylic acids, but these efforts have met with limited success because of the insolubility and toxicity of the esterified compounds.

Thus, chelators such as EDTA typically remain extracellularly or outside of cells. By way of illustration, orally administered EDTA reaches only very low concentrations outside cell surfaces in the body and for brief periods of time, while intravenous infusions result in much higher levels, and can be maintained for several hours. However, intravenously administered

EDTA can only chelate unwanted metals and toxins, if, e.g. they travel out of cell walls by diffusion. In contrast, this is not believed to occur to a significant extent – if at all – with chelators such as EDTA when taken by mouth. In sum, neither traditional approach achieves significant intracellular levels of chelating agents, and is thus unable to readily exert its actions intracellularly.

The preparations of the present invention comprise antioxidants that have effects that may be additive or synergistic to the effects of chelators such as EDTA; however, these antioxidants may be lipophilic. Because many parenterally suitable fluids such as saline, dextran, blood, stabilized hemoglobin solutions, etc., are all aqueous solutions, a problem with therapies based on lipid soluble antioxidants, such as .alpha.-lipoic acid, is the poor water solubility of these ingredients. The solubility may be enhanced by adding benzyl alcohol or DMSO, but such solvents introduce additional side effects.

Previous methods of delivering lipophilic antioxidants that involved solubilizing the antioxidant in solvents such as benzyl alcohol, DMSO, or other chemicals not only have the potential to introduce new toxicities, e.g. they may exacerbate microvascular injury, but the presence of these solvents confuses the interpretation of any protocol designed to evaluate antioxidant effects.

This invention provides novel solutions to these and other problems.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for transferring at least two ingredients, comprising an antioxidant and a chelating agent, across a cellular membrane.

Another object of the present invention is to provide a means for introducing at least two ingredients, comprising an antioxidant and a chelating agent, into the interior of a cell.

It is another object of the present invention to provide a method for introducing at least two ingredients, comprising an antioxidant and a chelating agent, into the interior of a cell of a living organism by introducing the at least two ingredients to the organism and carrying it to the cell in the blood stream. In a preferred but non-limiting aspect, the at least two ingredients are introduced by oral administration.

Another object of the present invention is to provide a method for the removal of intracellularly deposited toxic heavy metals.

Still another object of the present invention is to provide a therapy method for toxic heavy metal poisoning whereby both intracellularly deposited toxic heavy metals as well as extracellularly deposited toxic heavy metals can be removed from the body. In separate aspect, said body is a human body or an animal body (e.g. a pet or other raised animal).

TERMS

Biologically active and bioactive are used interchangeably, and can refer to in vitro as well as to in vivo situations.

Physiologic solutions suitable for intravenous injection include: e.g. Saline. In lieu of normal saline, other pharmaceutically acceptable solutions may be utilized including, but not limited to, 0.9% saline solution, 5% dextrose solution, lactated Ringer's solution, 5% dextrose in lactated Ringer's solution, dextrose-saline combinations, albumin-containing solutions, dextran, dextran-saline combinations, etc.

POEBACA: preparation(s) of encapsulated bioavailable chelating agents(s). Both plural and singular meanings are included.

POEBACAI: ingredient(s) for making up (a) preparation(s) of encapsulated bioavailable chelating agents(s). POEBACAI can exist in encapsulated form or in nonencapsulated form (e.g. a pre-encapsulated stage). Both plural and singular meanings are included.

1 ounce (oz.) = 28.3495231 grams (gm)

128 ounces = 1 gallon

DETAILED DESCRIPTION OF THE INVENTION

Ingredients.

This invention provides novel preparations of encapsulated bioavailable chelating agents (POEBACA), wherein in each of different preferred embodiments a POEBACA is comprised of the following ingredients (or PEOBACA), for which non-limiting examples are listed in Table 1:

- a) one or more members selected from Group A (e.g. alpha lipoic acid);
 - b) one or more members selected from Group B (e.g. EDTA);
 - c) one or more members selected from Group C (e.g. lecithin);
 - d) optionally, in separate embodiments, one or more members selected from Group D (e.g. magnesium chloride);
 - e) optionally, in separate embodiments, one or more members selected from Group E (glutathione);
 - f) optionally, in separate embodiments, one or more members selected from Group F (e.g. vinpocetine);
 - g) optionally, in separate embodiments, one or more members selected from Group G (e.g. nitrogen gas);
- wherein the ingredients are prepared in a manner that provides the encapsulation of a significant fraction of one or more ingredient(s) into liposomes or micropsheres.

Preferred numbers of Group A members (e.g. alpha lipoic acid).

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group A, where $n = 1, 2, 3, \dots, 100$, including every integer value within the range of 1 to 100. Thus, there are at least 100 embodiments of POEBACA, differing in that the minimum number of members selected from Group A that is contained in each embodiment ranges from one to one hundred (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 100. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group A; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group A; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group A; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least one hundred members selected from Group A; for convenience these are referred to as preferred embodiments A1 to A100, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Preferred numbers of Group B members (e.g. EDTA).

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group B, where $n = 1, 2, 3, \dots, 100$, including every integer value within the range of 1

to 100. Thus, there are at least 100 embodiments of POEBACA, differing in that the minimum number of members selected from Group B that is contained in each embodiment ranges from one to one hundred (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 100. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group B; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group B; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group B; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least one hundred members selected from Group B; for convenience these are referred to as preferred embodiments B1 to B100, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Preferred numbers of Group C members (e.g. lecithin).

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group C, where $n = 1, 2, 3, \dots, 100$, including every integer value within the range of 1 to 100. Thus, there are at least 100 embodiments of POEBACA, differing in that the minimum number of members selected from Group C that is contained in each embodiment ranges from one to one hundred (with every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 100. Thus, one preferred

embodiment of this invention provides a POEBACA comprised of at least one member selected from Group C; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group C; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group C; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least one hundred members selected from Group C; for convenience these are referred to as preferred embodiments C1 to 100, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Preferred numbers of Group D members (e.g. magnesium chloride).

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group D, where $n = 1, 2, 3, \dots, 20$, including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group D that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group D; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group D; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group D; etc. ;

another preferred embodiment of this invention provides a POEBACA comprised of at least twenty members selected from Group D; for convenience these are referred to as preferred embodiments D1 to D20, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Preferred numbers of Group E members (e.g. glutathione).

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group E, where $n = 1, 2, 3, \dots, 20$, including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group E that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group E; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group E; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group E; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least twenty members selected from Group E; for convenience these are referred to as preferred embodiments E1 to E20, and are intended to be claimed subject matter according to this invention.

Preferred numbers of Group F members (e.g. vinpocetine).

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group F, where $n = 1, 2, 3, \dots, 20$, including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group F that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group F; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group F; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group F; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least twenty members selected from Group F; for convenience these are referred to as preferred embodiments F1 to F20, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Preferred numbers of Group G members (e.g. nitrogen gas).

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group G, where $n = 1, 2, 3, \dots, 20$, including every integer value within the range of 1

to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group G that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group G; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group G; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group G; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least twenty members selected from Group G; for convenience these are referred to as preferred embodiments G1 to G20, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

Preferred numbers of members from Groups A through G.

This invention further provides the additional preferred aspects that result from all the possible combinations and permutations of the preferred embodiments of A1 to A100, B1 to B100, C1 to C100, D1 to D20, E1 to E20, F1 to F20, and G1 to G20. By way of illustration, (100 preferred embodiments corresponding to A1 to A100) x (100 preferred embodiments corresponding to B1 to B100) x (100 preferred embodiments corresponding to C1 to C100) x (20 preferred embodiments corresponding to D1 to D20) x (20 preferred embodiments corresponding to E1 to E20) x (20 preferred embodiments corresponding to F1 to F100) x (100 preferred embodiments corresponding to G1 to G20) = 160,000,000,000 or one hundred

and sixty billion preferred aspects, and these separate aspects are intended to be the subject matter of separate claims according to this invention.

Preferred amounts of ingredients.

Furthermore, the relative amounts of each ingredient that can comprise a POEBACA according to this invention are illustrated in Table 2. In separate embodiments, this invention provides all the physically possible combinations and permutations of ingredient amounts that listed in Table 2. Thus, this invention provides that the relative amounts of these ingredients can vary (as illustrated in Table 2), yielding additional aspects. Therefore, when considering the claim limitations regarding the relative amount of ingredients, the number of preferred embodiments is greater, by orders of magnitude, than 160,000,000,000 or one hundred and sixty billion preferred embodiments that don't specify amounts of ingredients, and all these preferred embodiments are intended to be the subject matter of separate claims according to this invention.

Table 1 Ingredients

Group	Group Members (Non-limiting examples are listed for each group)
A	<p><u>Antioxidants and hydrophobic ingredients</u></p> <p>R-(+)-.alpha.-lipoic acid (substantially enantiomerically pure), S-(-)-.alpha.-lipoic acid (substantially enantiomerically pure), R/S-.alpha.-lipoic acid (racemic mixture), R/S-.gamma.-lipoic acid (racemic mixture), other isomers of alpha lipoic acid, derivatives of alpha lipoic acid (such as the dihydro version of these alpha lipoic acid isomers, also known as dihydrolipoic acid or DHLA), animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, suncreening agents, vitamins, ferulic acid</p>
B	<p><u>Chelators</u></p> <p>EDTA, EGTA, DPTA, TTHA, HEDHA, NOTA, DOTA, HEDTA, other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl, and derivatives thereof</p>
C	<p><u>Phospholipids, lipids and fatty acids</u></p> <p>lecithin, phophatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids (e.g. palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, etc.), glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins (high or low density), cholesterol, and other lipids and polymerized lipids.</p>
D	<p><u>Magnesium Salts</u></p> <p>Magnesium chloride, Magnesium Gluconate, Magnesium Carbonate, Calcium Magnesium Citrate, Magnesium Sulfate</p>
E	<p><u>Sulfur-Containing Amino Acids, Sulfur-Containing Peptides, Sulfur-Containing Proteins</u></p> <p>Glutathione, methionine, cysteine</p>
F	<p>Plant alkaloids (e.g. vinpocetine, vincamine), coenzyme Q10, and analogues coenzyme Q10 (e.g. idebenone)</p>
G	<p><u>Gaseous ingredient</u></p> <p>Nitrogen gas, oxygen gas, atmospheric air, gaseous mixtures containing nitrogen gas, gaseous mixtures containing oxygen gas.</p>

Table 2. Amounts of ingredients (normalized to 2 oz or approximately 56 grams)

Group (with example of a group member)	Example 1 (Absolute amount, mg)	Example 1 (Relative amount, %)	Preferred amounts intended for protection according to this invention (both individually and collectively as a group)
A (e.g. alpha lipoic acid)	100.0 mg	0.17	From about 0.01 mg to about 20,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B (e.g. EDTA)	1,000.0 mg	1.7	From about 0.01 mg to about 30,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
C (e.g. lecithin)	30,000.0 mg	50.0	From about 0.01 mg to about 40,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
D (e.g. magnesium chloride)	150.0 mg	0.26	From about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
E (e.g. glutathione)	1,000mg	1.7	From about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
F (e.g. vinpocetine)	100 mg	0.17	From about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
Example 1. Other ingredients: Water (30 – 40%), Ethanol (5 – 15 %), Gum Arabic (0.5 – 2%), Flavorings (0 – 5 %).			

In Table 2 the relative amounts of each ingredient (POEBACAI) have been expressed in the context of a 2 ounce dose. This is for convenience and consistency, but in separate embodiments this invention provides that that dosages or other sizes can be prepared and administered, particularly ranging, by way of non-limiting exemplification, from about 0.1 ounce to about 128 ounces (or one gallon), including every 0.1 ounce increment in between.

Preferred amount(s) of Group A members (e.g. alpha lipoic acid).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group A (e.g. alpha lipoic acid) collectively is preferably from about 0.01 mg to about 20,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group A ingredient(s) individually is preferably from about 0.01 mg to about 20,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Thus; by way of illustration:

- 1) in one embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is preferably 0.01 mg;
- 2) in another embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is preferably 0.02 mg;

3) in another embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is preferably 0.03 mg; etc. ;

and

2,000,000) in another embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is preferably 20,000 mg.

Thus, there are at least 2,000,000 preferred embodiments. This is illustrated in Table 2.

Preferred amount(s) of Group B members (e.g. EDTA).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group B (e.g. EDTA) collectively is preferably from about 0.01 mg to about 30,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group B ingredient(s) individually is preferably from about 0.01 mg to about 30,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Preferred amount(s) of Group C members (e.g. lecithin).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group C (e.g. lecithin) collectively is preferably from about 0.01 mg to about 40,000 mg inclusive, including specifically each increment of about 0.01 mg within

this range. Furthermore, this invention provides separate embodiments wherein per 2 fluid ounces the total amount of each specific Group C ingredient(s) individually is preferably from about 0.01 mg to about 40,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Preferred amount(s) of Group D members (e.g. magnesium chloride).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group D (e.g. magnesium chloride) collectively is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group D ingredient(s) individually is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Preferred amount(s) of Group E members (e.g. glutathione).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group E (e.g. glutathione) collectively is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 fluid ounces the total amount of each specific Group E ingredient(s) individually is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Preferred amount(s) of Group F members (e.g. vinpocetine).

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group F (e.g. vinpocetine) collectively is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group F ingredient(s) individually is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Preferred percentages of encapsulated Group G members (e.g. nitrogen gas).

This invention provides separate embodiments wherein one or more gases may be contained in a percentage of the liposomes or micropsheres in a POEBACA. In separate embodiments, the percent of liposomes or micropsheres that contains a gas is from about 1% to about 100%, including every integer value in between.

Preferred methods of administration.

This invention provides POEBACA that can be administered by several routes, including intravenous, topical, and oral. Furthermore, in separate embodiments, this invention provides forms of POEBACA that can be administered by inoculation or injection, (e.g., intraperitoneal, intramuscular, subcutaneous, intra-aural, intra-articular, intra-mammary, etc.), topical application (e.g., on areas, such as eyes, ears, skin or on afflictions such as wounds, burns, etc.), and by absorption through epithelial or mucocutaneous linings (e.g. vaginal and other epithelial linings, gastrointestinal mucosa, etc.). Methods are known for making

POEBACA containing liposomes that are suitable for each of these methods of administration as well as other methods of administration that are known in the art.

For example, in preferred embodiments, this invention provides POEBACA in liquid forms that can be administered orally. The POEBACA can be also prepared as capsules, tablets, pellets (e.g. for animal consumption), suppositories, or creams and ointments. The POEBACA can be also prepared as physiological solutions suitable for i.v. administration or other parenteral administration.

In as many separate aspects, this invention also provides all the possible combinations of ingredient quantities that are possible (e.g. the total of all the ingredients or POEBACAI does not surpass 100% of the relevant total dosage of the POEBACA, and admixing or solubility limitations are not exceeded).

Preferred percentages of ingredients that are contained in liposomes or micropsheres. In separate aspects, this invention also provides that a POEBACA may include ingredients (or POEBACAI) that are not contained in micropsheres or liposomes in addition to ingredients that are contained in liposomes, and that these ingredients may be the same or different substances.

In separate aspects, this invention also provides that for each ingredient (or POEBACAI) the percent that is contained in micropsheres or liposomes (in contrast to the percentage that is not contained in micropsheres or liposomes, but rather is in solution) may be from about

0.1% to about 100.0%, including every 0.1% increment within this range. This provides at least about 1000 separate aspects that are intended for protection according to this invention.

In separate aspects, this invention also provides that in a single POEBACA, the microspheres or liposomes may be fairly homogeneous in size or in content; alternatively they may be fairly heterogeneous in size or in content.

Preferred Group A members (e.g. alpha lipoic acid).

Group A members include: antioxidants, particularly hydrophobic antioxidants and other hydrophobic ingredients.

Group A members include, but are not limited to:

R-(+)-.alpha.-lipoic acid (substantially enantiomerically pure), S-(-)-.alpha.-lipoic acid (substantially enantiomerically pure), R/S-.alpha.-lipoic acid (racemic mixture), R/S-.gamma.-lipoic acid (racemic mixture), other isomers of alpha lipoic acid, derivatives of alpha lipoic acid (such as the dihydro version of these alpha lipoic acid isomers, also known as dihydrolipoic acid or DHLA), animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sunscreens agents, vitamins, ferulic acid.

Group A members also include, but are not limited to:

fatty acids, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing

sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, and polymerized lipids.

Preferred Group B members (e.g. EDTA).

Group B members include: chelators or chelating agents.

Group B members include, but are not limited to:

EDTA, EGTA, DPTA, TTHA, HEDHA, NOTA, DOTA, HEDTA, other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl, and derivatives thereof. According to this invention, other chelators that are members of Group B are provided herein or are otherwise known in the art and can serve as ingredients for this invention.

Preferred Group C members (e.g. lecithin).

Group C members include: phospholipids, lipids and fatty acids.

Group C members include, but are not limited to:

lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids (e.g. palmitic acid, stearic acid,

oleic acid, linolenic acid, linoleic acid, etc.), glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins (high or low density), cholesterol, and other lipids and polymerized lipids.

Preferred Group D members (e.g. magnesium chloride).

Group D members include: magnesium salts.

Group D members include, but are not limited to:

magnesium chloride, magnesium gluconate, magnesium carbonate, calcium magnesium citrate, magnesium sulfate, other salts of magnesium, and other forms of magnesium.

Preferred Group E members (e.g. glutathione).

Group E members include: sulfur-containing amino acids, sulfur-containing peptides, sulfur-containing proteins, and other sulfur-containing substances.

Group E members include, but are not limited to:

magnesium chloride, magnesium gluconate, magnesium carbonate, calcium magnesium citrate, magnesium sulfate, other salts of magnesium, and other forms of magnesium

Preferred Group F members (e.g. vinpocetine).

Group F members include: Vinpocetine, vincamine, idebenone

Preferred Group G members (e.g. nitrogen gas).

Group G members include: Nitrogen gas, atmospheric air, and other mixtures of gases that contain nitrogen, oxygen, mixtures of gases that contain oxygen, argon, and mixtures of gases that contain argon, etc.

Lipophilic Anti-oxidants (e.g. alpha lipoic acid). Alpha-lipoic acid, in addition to its non-toxicity and lipophilicity, has the advantage of being rapidly converted in tissues into its reduced form, dihydrolipoic acid (DHLA). DHLA also has potent antioxidant effects. Further, both .alpha.-lipoic acid and DHLA have been shown to disarm oxidants through a variety of mechanisms including free radical quenching, metal chelation, and regeneration of other common natural antioxidants.

In one embodiment, the present invention provides a lipophilic antioxidant in an aqueous physiological fluid, such as a resuscitation fluid by lipid encapsulation, e.g. by providing liposomal formation methods to form stable micellular solutions of .alpha.-lipoic acid or other lipophilic antioxidant(s).

The present invention seeks to overcome previous limitations by solubilizing .alpha.-lipoic acid in aqueous solution without the use of solvents such as harsh organic solvents. .alpha.-lipoic acid and other antioxidants are rendered soluble in aqueous solutions by the use of liposomal formation processes, such as ultrasonication. Because the .alpha.-lipoic molecule contains a polar (water soluble) carboxy-acid group and a non-polar, lipid soluble chain of carbon and sulfur atoms, the molecule is amphipathic, i.e., it has the ability to form micelles. Micelles may be formed in aqueous solution if a molecule possesses both polar and non-polar

groups. After ultrasonication the polar, a number of the water soluble ends of the .alpha.-lipoic acid molecule are on the outside of aggregations of .alpha.-lipoic acid. A number of the non-polar, lipid soluble tails are directed inward forming a tiny droplet, a micelle, which is water soluble. Ultrasonication of amphipathic molecules into micelles such as can be done with .alpha.-lipoic acid also has the possibility of creating mixed micelles. In this manner a mixture of .alpha.-lipoic acid with other antioxidants, which may not have the ability to form micelles alone for lack of any polar group, can be contained within a micelle of .alpha.-lipoic acid. In this way, mixed micelles containing .alpha.-lipoic acid and purely non-polar but highly lipid soluble antioxidants can be used to convey antioxidants to the tissues.

There are numerous other clinical conditions besides hemorrhagic shock which have as their final common pathway oxidant-inducing injury to tissues which can be treated and/or prevented with the inventive solutions.

CHELATING AGENTS

According to this invention, the polyaminopolycarboxylic acid, EDTA (ethylene-diaminetetraacetic acid) is provided as a chelating agent for removing toxins such as heavy metals. Additionally, a related polyaminopolycarboxylic acid, diethylenetriaminepentaacetic acid (DTPA) is also provided as a chelating agent that has been shown to have an ability to remove various heavy metals.

According to this invention, EGTA (ethyleneglycol-bis[.beta.-aminoethyl ether]-N,N'-tetraacetic acid) is also provided as chelating agent. EGTA is more specific for particular substances such as calcium when compared to other substances such as magnesium, and thus may be used as a preferred ingredient when it is desirable to chelate calcium (e.g. as is found in arterial plaques, and thus for diminishing arterial plaques) more than for chelating magnesium.

DMSA (dimercaptosuccinic acid) is one effective oral chelating agent that is absorbed orally, and is more effective at chelating particular substances such as mercury, lead, and arsenic in comparison to other substances; and thus DMSA may be used as a preferred ingredient when it is desirable to chelate mercury lead and arsenic (such for the detoxification of poisoning from lead or mercury r arsenic) more than for chelating other substances.

According to this invention, other useful chelating agents are also provided, including diethylenetriamine-pentaacetic acid (DTPA), triethylenetetraaminehexaacetic acid (TTHA), N-hydroxyethylenediaminehexaacetic-acid (HEDHA), 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), and N'hydroxyethylenediamine-N,N,N'-triacetic acid (HEDTA).

According to this invention, preferred chelating agents also include iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl

acetoacetate), 2,2'-dipyridyl. IDA is a preferred chelating headgroup which is selective for copper ions.

Preferable chelators for use in the present invention include, but are not limited to, ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium, trisodium, tetrasodium, dipotassium, tripotassium, dilithium and diammonium salts of EDTA; the barium, calcium, cobalt, copper, dysprosium, europium, iron, indium, lanthanum, magnesium, manganese, nickel, samarium, strontium, and zinc chelates of EDTA; trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid monohydrate; N,N-bis(2-hydroxyethyl)glycine; 1,3-diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; ethylenediamine-N,N'-diacetic acid; ethylenediamine-N,N'-dipropionic acid dihydrochloride; ethylenediamine-N,N'-bis(methylenephosphonic acid) hemihydrate; N-(2-hydroxyethyl)ethylenediamine-N,N,N',N'-triacetic acid; ethylenediamine-N,N,N',N'-tetrakis(methylenephosphonic acid); O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid; N,N-bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid; 1,6-hexamethylenediamine-N,N,N',N'-tetraacetic acid; N-(2-hydroxyethyl)iminodiacetic acid; iminodiacetic acid; 1,2-diaminopropane-N,N,N',N'-tetraacetic acid; nitrilotriacetic acid; nitrilotripropionic acid; the trisodium salt of nitrilotris(methylenephosphoric acid); 7,19,30-trioxa-1,4,10,13,16,22,27,33-octaazabicyclo[11,11,11] pentatriacontane hexahydrobromide; and triethylenetetramine-N,N,N',N'',N''',N''''-hexaacetic acid. It is contemplated that any chelator which binds barium, calcium, cerium, cobalt, copper, iron, magnesium, manganese, nickel, strontium, or zinc will be acceptable for use in the present invention.

More preferably, the chelators for use in conjunction with the present invention may include ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium, trisodium, tetrasodium, dipotassium, tripotassium, dilithium and diammonium salts of EDTA; 1,3-diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid; and 7,19,30-trioxo-1,4,10,13,16,22,27,33-octaazabicyclo[11,11,11] pentatriacontane hexahydrobromide.

Most preferably, the chelators for use in the present invention may include ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium salt of EDTA; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; and O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid.

In a preferred embodiment this invention provides a preparation (or POEBACA), wherein said chelator in said POEBACA may be selected from the group of chelators consisting of EDTA free acid, EDTA 2Na, EDTA 3Na, EDTA 4Na, EDTA 2K, EDTA 2Li, EDTA 2NH₄, EDTA 3K, Ba(II)-EDTA, Ca(II)-EDTA, Co(II)-EDTA, Cu(II)-EDTA, Dy(III)-EDTA, Eu(III)-EDTA, Fe(III)-EDTA, In(III)-EDTA, La(III)-EDTA, Mg(II)-EDTA, Mn(II)-EDTA, Ni(II)-EDTA, Sm(III)-EDTA, Sr(II)-EDTA, Zn(II)-EDTA, CyDTA, DHEG, DTPA-OH, DTPA, EDDA, EDDP, EDDPO, EDTA-OH, EDTPO, EGTA, HBED, HDTA, HIDA, IDA, Methyl-EDTA, NTA, NTP, NTPO, O-Bistren, and TTHA.

Preferred chelating agents may also be selected from ethylenebis (oxyethylene nitrilo)tetraacetic acid (EGTA) and ethylene diamine tetracetic acid (EDTA), sodium citrate, or oxalate salts such as sodium, potassium, ammonium or lithium oxalate.

Preferred chelating groups include those derived from polyamino-polycarboxylic groups, e.g. those derived from EDTA, DTPA, DOTA, TETA, TITRA or 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (HMPAO) or from such groups substituted, e.g. by a p-isothiocyanato-phenyl or 1-3 alkyl, preferably p-isothiocyanatobenzyl. Chelating groups derived from DTPA are also preferred.

In a preferred embodiment this invention provides a preparation (or POEBACA), wherein the chelating group is derived from ethylene diaminetetraacetic acid (EDTA), diethylene triamine pentaacetic acid (DTPA), ethylene glycol-0,0'-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), N,N'-bis(hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED), triethylenetetramine hexaacetic acid (TTHA), substituted EDTA or -DTPA 1,4,7,10-tetra-azacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) and 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), in free form or in pharmaceutically accepted salt form.

In a preferred embodiment this invention provides a preparation (or POEBACA), wherein the chelating group is derived from 1,4,7,10-tetraazacyclotridecane-1,4,7,10-tetraacetic acid (TITRA), 1,4,8,11-tetraazacyclotetradecane (TETRA); EDTA, DTPA, DOTA, TETA, TITRA, TETRA or 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (HMPAO)

substituted by p-isothiocyanato-phenyl-C.sub.1-3 alkyl, in free form or in pharmaceutically accepted salt form.

In a preferred embodiment this invention provides a preparation (or POEBACA), comprising R/S-.gamma.-lipoic acid (6,8-dimercaptooctanoic acid) or R/S-.alpha.-lipoic acid (D,L-thioctic acid).

According to separate but non-limiting embodiments of this invention, "substantially enantiomerically pure" 1,2-dithiolane-3-pentanoic acid (thioctic acid, .alpha.-lipoic acid) is within the range from at least about 80% pure to at least about 99% pure inclusive as well as every 1% increment within this range (i.e. at least about 80% pure, at least about 81% pure, at least about 82% pure, etc.).

According to another embodiment of this invention, D,L-thioctic acid can be used in the form of the racemic mixture. According to this invention, a racemic mixture can be comprised of two isomers that are found at a ratio within the range from about 20%:80 % to about 80%:20% inclusive as well as every 1% increment within this range (i.e. about 20%:80%, about 21%:79%, about 22%:78%, etc.).

According to another embodiment of this invention, optically active R-(+)-.alpha.-lipoic acid is used. R-(+)-.alpha.-lipoic acid is a natural substance that is found in animals and humans, and it acts as coenzyme in the oxidative decarboxylation of .alpha.-keto acids.

Microspheres

Specific, but non-limiting, examples of microspheres according to this invention are provided herein. Specific, but non-limiting, examples of ways of making, administering, and using microspheres according to this invention are provided herein. In separate non-limiting embodiments, this invention provides that the microspheres can be made using lecithin (and/or alternative ingredients as per Table 1 and 2) in amounts in the range from about 0.1 gram to about 40 grams inclusive, including specifically each increment of about 0.1 gram within this range, in a total of 2 ounces of final POEBACA product.

In one embodiment, this invention provides POEBACA comprising gas-filled microspheres. The invention further relates to methods for employing such microspheres as delivery systems to deliver the POEBACA.

In one embodiment, this invention provides POEBACA comprising at least one member selected from the group consisting of animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sunscreens agents, vitamins, alpha lipoic acid, ferulic acid, and flavors and said solid or semi-solid oil component is at least one member selected from the group consisting of animal and vegetable oils, hydrocarbon oils, ester oils, higher fatty acids, higher alcohols, waxes, sunscreens agents and flavors

Example 2

	INGREDIENTS:	per 2 fl oz	%
	Lecithin	30.0 gm	50
	EDTA (e.g. Disodium EDTA)	1.0 gm	1.7
	Magnesium Chloride	150.0 mg	0.26
	Alpha Lipoic Acid	100.0 mg	0.17
	Purified Water		37.3
	Ethyl Alcohol		10
	Gum Arabic		0.5

- 1) Dissolve alpha lipoic acid and EDTA in half the amount of alcohol.
- 2) Disperse lecithin in half the amount of alcohol and equal amount of water
Heat to 50C, mix with high shear mixing or sonication (sufficient to form micropsheres or liposomes) for 20 minutes, cool to 40C.
- 3) Add magnesium chloride and gum arabic to the remaining amount of water,
Stir for 30 minutes at room temperature
- 4) Add step number 3 to step number 2. Mix for 20 minutes
- 5) Add step 4 to step 1, stir gently for 20 minutes.
- 6) Take a random samples and test for the presence of liposomes.

Example 3

	INGREDIENTS:	per 2 fl oz	%
	Lecithin	30.0 gm	50
	EDTA (e.g. Disodium EDTA)	1.0 gm	1.7
	Magnesium Chloride	150.0 mg	0.26
	Alpha Lipoic Acid	100.0 mg	0.17
	Purified Water		37.3
	Ethyl Alcohol		10
	Gum Arabic		0.5

- 1) Dissolve alpha lipoic acid in half the amount of alcohol.
- 2) Disperse lecithin in half the amount of alcohol and equal amount of water
Heat to 50C, mix with high shear mixing or sonication (sufficient to form micropsheres or liposomes) for 20 minutes, cool to 40C.
- 3) Add EDTA, magnesium chloride and gum arabic to the remaining amount of water,
Stir for 30 minutes at room temperature
- 4) Add step number 3 to step number 2. Mix for 20 minutes
- 5) Add step 4 to step 1, stir gently for 20 minutes.
- 6) Take a random samples and test for the presence of liposomes.

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

In a preferred embodiment this invention provides a preparation (or POEBACA), comprising ocular drug delivery vehicle of an oil-in-water submicron emulsion consisting essentially of about 0.5 to 50% of a first component of an oil, about 0.1 to 10% of a second component of an emulsifier, comprising a phospholipid, about 0.05 to 5% of a non-ionic surfactant and an aqueous component, said submicron emulsion having a mean droplet size in the range of 0.05 to 0.5 μm , and a weight ratio of surfactant to oil of about 1:1 or less.

In a preferred embodiment this invention provides a method for transferring ingredients making up a preparation of encapsulated bioavailable chelating agents (i.e. POEBACAI) across a cellular membrane by encapsulating said ingredients within liposomes and carrying said POEBACAI to the cellular membrane where the liposomes will be taken up by the cells, thereby transferring the POEBACAI across the cellular membrane. POEBACAI can be introduced into the interior of a cell of a living organism wherein the liposomes will be decomposed, releasing the POEBACAI to the interior of the cell. The released POEBACAI will complex intracellularly deposited toxic heavy metals, permitting the more soluble metal complex to transfer across the cellular membrane from the cell and subsequently be removed from the living organism.

In a preferred embodiment this invention provides a method of transferring POEBACAI across a cellular membrane comprising: encapsulating said POEBACAI within liposomes; and carrying said liposome encapsulated POEBACAI to said cellular membrane, whereby said liposome encapsulated POEBACAI will transfer across said cellular membrane.

In a preferred embodiment this invention provides a method of introducing a POEBACAI into the interior of a cell in accordance with the method of claim 1 wherein said cellular membrane is the membrane wall of said cell and said encapsulated POEBACAI passes through the membrane wall of said cell into the interior of said cell, wherein said liposomes will be decomposed, thereby releasing said POEBACAI to the interior of said cell.

In a preferred aspect this invention provides a method wherein said cell is a cell of a living organism and said POEBACAI is carried to said cell by injecting a saline suspension of said liposome POEBACAI into the blood stream of said living organism whereby said POEBACAI is carried to the cell within the blood

In a preferred embodiment this invention provides a method for the removal of intracellularly deposited toxic heavy metals comprising:

encapsulating a POEBACAI agent within liposomes;

introducing said liposomal POEBACAI into the blood system by one or more of the following routes: oral administration, intravenous injection, transdermal patch; whereby

said liposome POEBACAI is carried to said body cells within said blood system;

said liposome POEBACAI is passed through the cell wall into the interior of said body cell;

said POEBACAI is released to the interior of said cell by the biological degradation of said liposome by lysosomal enzymes, said released POEBACAI complexing said intracellularly deposited toxic metal;

said complexed toxic metal is passed through the cell wall into said blood stream; and

said complexed toxic metal is removed from said blood stream and the body by normal body processes.

In a preferred embodiment this invention provides a preparation of POEBACA wherein said liposomes are prepared from a mixture of lecithin and cholesterol.

In a preferred embodiment this invention provides a POEBACAI comprised of a member chosen from the group consisting of EDTA, EGTA, and DTPA.

In a preferred embodiment this invention provides a detoxification method wherein said toxic heavy metals are selected from the group consisting of plutonium, gold, mercury, and lead, beryllium, and cadmium.

Any gel can be used in the practice of the present invention. The materials which can be used to form such gels include but are not limited to: carbohydrates such as cellulose, methylcellulose, starch and modified starch, agarose, gum arabic, ghatti, karay, tragacanth, guar, locust bean gum, tamarind, carageenan, alginate, xanthan, chickle, collagen, polyacrylamide, polysiloxanes (polyanhydrides, e.g., malic anhydride copolymers, polyacrylates, e.g., hydroxyethylpolymethacrylate polymethylmethacrylate, polyethylethacrylate polymethacrylate, ethylenevinylacetate copolymers, ethylenevinylalcohol copolymers, polyorthoesters, .epsilon.-caprolactones, amino acid polymers such as gelled albumin, amino acid polymers and copolymers and gelatins, and other organic or inorganic polymers which can be mixed with liposomes in vitro.

After the mixture forms a gel the resulting liposome-gel matrix can be implanted in tissues. In a particularly useful embodiment of the present invention soft gel matrices such as agarose, collagen and the like containing sequestered liposomes may be injected in vivo. Alternatively, gels such as methylcellulose can be formed in the tissues after inoculation of liposomes in a suspension containing the gel material. After inoculation the suspension forms a gel and the liposomes remain sequestered in the gel matrix rather than dispersed and cleared. Regardless of the method used for preparing and implanting the gel matrix, the release of a liposome entrapped bioactive chelating agent or other POEBACAI is prolonged and the relative concentration of the agent at the site of inoculation is increased.

Virtually any POEBACAI (including chelating agents) as well as virtually any other bioactive agent can be entrapped within the liposomes for use according to the present

invention. Such agents include but are not limited to antibacterial compounds, antiviral compounds, antifungal compounds, anti-parasitic compounds, tumoricidal compounds, proteins, toxins, vitamins, trace minerals, heavy metals, enzymes, hormones, neurotransmitters, lipoproteins, glycoproteins, immunoglobulins, immunomodulators, dyes, radiolabels, radio-opaque compounds, fluorescent compounds, polysaccharides, cell receptor binding molecules, anti-inflammatories, antiglaucomic agents, mydriatic compounds, anesthetics, nucleic acids, polynucleotides, etc.

In fact, if concurrent therapy is desired, two or more POEBACAI (including chelating agents) or other bioactive agents may be entrapped in one liposome population which is sequestered in the gel matrix. Alternatively, two or more liposome populations (of the same or different types of liposomes, e.g. mixtures of SPLVs, MPVs, SUVs, LUVs, REVs, etc.) which each entrap the same or different POEBACAI (including chelating agents) or other bioactive chelating agents may be sequestered in the gel matrix.

In yet another embodiment of the present invention the gel can be used as a vehicle for the same or different bioactive chelating agents and other POEBACAI than those entrapped by liposomes.

In certain therapeutic applications it may be desired to deliver a relatively high dose of a drug compound (i.e., compound A) followed by a sustained dose of the same or another compound (i.e., compound B). According to the present invention, this is readily accomplished by entrapping compound B in liposomes, sequestering the liposomes in a gel

matrix containing compound A, and administering the same in vivo in a single inoculation. Thus, rapid delivery of compound A by diffusion from the gel, and slow sustained delivery of compound B by release from the liposomes is effected

The release of the bioactive chelating agents may be controlled by the type of liposomes used and the membrane composition of the liposome bilayers as well as by the type and porosity of the gels used. The rate of release is also dependent upon the size and composition of the bioactive chelating agent itself. The liposome itself is the first rate limiting factor in the release of entrapped bioactive chelating agents. The rate of release may depend upon the number of bilayers, the size of the liposomes and most importantly the bilayer composition.

A number of researchers add "stabilizers" such as sterols, cholesterol and the like to the phospholipid bilayers in order to alter the permeability of the liposome (Papahadjopoulos, D., Kimilberg, H. K., 1974, in Progress in Surface Science, ed. S. G. Davison, pp. 141-232, Oxford: Pergamon; Demel, R. A., Bruckdorf, K. R., Van Deenan, L. L., 1972, Biochem. Biophys. Acta, 255:331-347). For the present invention it is important that the stable liposomes will release their contents upon contact with body fluids or culture media. The rate of release may be controlled by modifying liposome membranes accordingly using known methods.

Use of the Liposome-Gel Preparation in Living Systems.

The liposome-gel compositions of the present invention may be used for sustained delivery of a bioactive chelating agent to cells and/or fluids in vivo and in vitro.

When used in vivo, the liposome-gel compositions of the present invention may be administered before or after gel formation. Routes of administration include but are not limited to: inoculation or injection, (e.g., intraperitoneal, intramuscular, subcutaneous, intra-aural, intra-articular, intra-mammary, etc.), topical application (e.g., on areas, such as eyes, ears, skin or on afflictions such as wounds, burns, etc.), and by absorption through epithelial or mucocutaneous linings (e.g. vaginal and other epithelial linings, gastrointestinal mucosa, etc.).

For example the liposome-gel preparations of the present invention may be inoculated in vivo to provide for the sustained systemic release of the bioactive chelating agent. Such applications may be particularly useful for the systemic release of drugs such as hormones (e.g., to control growth, fertility, sugar metabolism, etc.) or antimicrobials to control and treat infections, etc.

In an alternative example, the liposome-gel preparation may be applied topically. Topical application may be particularly useful for the treatment of wounds (either surgical or non-surgical wounds) where the sustained release of POEBACAI (including chelating agents), antimicrobials and/or blood clotting factors may be helpful in the healing process. Similarly, the liposome-gel preparation may be topically applied to burns for the sustained release of

POEBACAI (including chelating agents), antimicrobials and/or cell growth factors. The liposome-gel preparation may also be applied in the ear to treat infections by providing sustained release of POEBACAI (including chelating agents), antimicrobials; this would reduce the necessity of repeated applications of the bioactive chelating agent in the form of ear drops.

In another alternative embodiment, a liposome-gel preparation may be administered orally for sustained release. Such application may be useful for sustained release to oral epithelium and other oral tissues and for sustained release to epithelia of the alimentary tract.

The liposome-gel preparations of the present invention may also be used in vitro to provide for sustained release of a POEBACAI (including chelating agents) into the cell or tissue culture medium. Such POEBACAI (including chelating agents) may also include but are not limited to nutrients, drugs, hormones, growth factors, etc. The liposome-gel preparation may be used as a support for cell adhesion and growth; for instance, a liposome-collagen gel may be especially useful for culturing muscle cells, nerve cell, or liver cells. When the liposome-gel preparation is applied as an overlay, a liposome-agarose gel may be particularly useful.

REFERENCES

Many methods for the preparation of micropsheres or liposomes are many in the art. For particularly useful references regarding liposome preparation, see U.S. patents listed below.

The following US patents are incorporated herein in their entirety:

5,000,887; 4,994,213; 4,981,692; 4,975,282; 4,963,297; 4,952,405; 4,944,948; 4,927,637;
4,927,571; 4,923,854; 4,906,476; 4,897,384; 4,895,719; 4,891,208; 4,885,172; 4,880,635;
4,873,088; 4,861,580; 4,839,175; 4,837,028; 4,828,837; 4,822,777; 4,818,537; 4,804,539;
4,781,871; 4,766,046; 4,762,915; 4,752,425; 4,737,323; 4,721,612; 4,714,571; 4,708,861;
4,698,299; 4,668,638; 4,666,831; 4,610,868; 4,588,578; 4,564,599; 4,522,803; 4,483,929

which are all incorporated by reference in their entirety.

Additional references that are also incorporated herein in their entirety include US patents:

5,990,153; 3,932,657;

ABSTRACT

This invention provides, in non-limiting embodiments, novel preparations of chelating agents encapsulated in micelles or liposomes comprising the triple combination of: 1) micelles or liposomes comprising alpha lipoic acid or a derivative thereof and 2) micelles or liposomes comprising a chelating agent, such as EDTA; and furthermore, in different embodiments, optionally 3) magnesium chloride. The micelles or liposomes may be comprised of what have been termed "essential phospholipids".

CLAIMS

1. A preparation of encapsulated bioavailable chelating agents comprised of the following ingredients:
 - a) one or more members selected from a first group consisting of: R-(+)-.alpha.-lipoic acid, S-(-)-.alpha.-lipoic acid, R/S-.alpha.-lipoic acid, R/S-.gamma.-lipoic acid, other isomers of alpha lipoic acid, dihydrolipoic acid or DHLA, animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sunscreens agents, vitamins, and ferulic acid; wherein at least 10% of said one or more members from said first group is in microspheres or liposomes; and
 - b) one or more members selected from a second group consisting of: EDTA, EGTA, DPTA, TTHA, HEDHA, NOTA, DOTA, HEDTA, other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetate (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl, and derivatives thereof; wherein at least 1% of said one or more members from said second group is in microspheres or liposomes; wherein at least 10% of said one or more members from said second group is in microspheres or liposomes; and
 - c) one or more members selected from a third group consisting of: lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin,

cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids, palmitic acid, stearic acid, oleic acid, linolenic acid, limoleic acid, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins, cholesterol, and other lipids or polymerized lipids; wherein at least 10% of said one or more members from said third group is in microspheres or liposomes; and

wherein said or more members selected from said first group, and said or more members selected from said second group members, and said or more members selected from said third group have been admixed and subjected to a procedure to create microspheres or liposomes.

2. A preparation of encapsulated bioavailable chelating agents comprised of the following ingredients:

- a) one or more members selected from a first group consisting of: R-(+)-.alpha.-lipoic acid (substantially enantiomerically pure), S-(-)-.alpha.-lipoic acid (substantially enantiomerically pure), R/S-.alpha.-lipoic acid (racemic mixture), R/S-.gamma.-lipoic acid (racemic mixture), other isomers of alpha lipoic acid, derivatives of alpha lipoic acid (such dihydrolipoic acid or DHLA); wherein at least 25% of said one or more members from said first group is in microspheres or liposomes; and
- b) one or more members selected from a second group consisting of: EDTA, EGTA, DPTA, TTHA, HEDHA, NOTA, DOTA, HEDTA, other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic

acid, crown ethers, nitrilotriacetic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl; wherein at least 25% of said one or more members from said second group is in microspheres or liposomes; and

c) one or more members selected from a third group consisting of:

lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid; wherein at least 25% of said one or more members from said third group is in microspheres or liposomes.